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Cardiovascular alterations in adult GH deficiency

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There is a growing body of evidence indicating that patients with adult GH deficiency (GHD) are characterized by a cluster of traditional and emerging cardiovascular risk factors and markers, which can significantly increase their cardiovascular morbidity and mortality possibly linked to aberrations in GH status. Patients with adult GHD present multiple different cardiovascular abnormalities. In addition, cardiovascular risk in adult GHD is increased due to altered body composition, abnormal lipid profile, insulin resistance and impaired glucose metabolism. Cardiovascular risk factors can be reversed, at least partially, after GH replacement. However, evidence on the effects of GH replacement on cardiovascular events and mortality is too limited in adult GHD patients. Aim of this review is to provide an at-a-glance overview of the role of the GH/IGF-I on the cardiovascular system and the state of art of the effects of GH replacement on cardiovascular system.

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Introduction

GH is principally involved in the regulation of somatic growth, including cardiac development and function, and exerts its effects either directly or indirectly by stimulating the production of its tissue effector insulin-like growth factor-1 (IGF-I), which ultimately mediates GH actions on peripheral tissues. In particular, GH/IGF-I axis plays an important role in cardiac growth, myocardial contractility and vascular system. Abnormalities of the GH/IGF-I axis contribute in determining cardiovascular disease, as suggested by clinical studies reporting an increased risk for cardiovascular morbidity and mortality both in GH deficiency (GHD) and excess [1–4].

Physiological effects of GH on cardiovascular system

As reported in previous reviews, the relationship between GH/IGF-I axis and cardiovascular system has been demonstrated by several experimental studies [4,5]. In physiological conditions, GH/IGF-I axis exerts relevant cardiovascular actions aimed to regulate cardiac growth and myocardial contractility, thus contributing to the maintenance of cardiac mass and function in normal adults [4]. Functional receptors for GH and IGF-I are also expressed in blood vessels [6]. Thus GH/IGF-I axis interacts specifically with the vascular system regulating the vascular tone and the peripheral resistance [4], which indirectly affects cardiac performance [5]. In addition, GH upregulates the myocardial expression of IGF-I mRNA [6]. Besides direct actions of GH, endocrine or autocrine/paracrine effects of locally produced IGF-I on the cardiovascular system are likely operating as well, thus making it difficult to differentiate between the direct effects of GH and those IGF-I-mediated [7].

GH and IGF-I receptors expressed in cardiomyocytes are responsible for direct actions of both hormones on cardiac growth and metabolism. However, the vast majority of the studies have failed to show direct, IGF-I-independent hypertrophic effects of GH on cardiomyocytes [4]. In contrast, experimental models clearly demonstrated that IGF-I *per se* causes hypertrophy of cultured rat cardiomyocytes [8]. The increased cardiac protein synthesis is mainly mediated by the activation of the phosphatidylinositol 3-kinase (PI3K)–Akt pathway, one of the two major pathways of IGF-I signalling [9], and by delaying cardiomyocyte apoptosis [10]. GH and IGF-I also have direct effects on myocardial contractility and cardiac output in both humans and experimental animals. These effects are mediated by the increased mRNA expression for specific muscle proteins, including troponin, myosin light chain-2, and α-actin [4,5]. GH promotes the shift toward the V3 myosin isoform with lower ATPase activity, which may decrease the energy demand of the contractile process [4,5,11]. In addition, GH and IGF-I increase both intracellular calcium content and calcium sensitivity of myofilaments in cardiomyocytes [4,11]. The endothelial cells have high-affinity binding sites for IGF-I. In particular, the local production of IGF-I causes endothelial dependent vasodilatation via the stimulation of the nitric oxide (NO) production [4]. Moreover, IGF-I may cause vasodilatation through non-endothelium-dependent actions, by increasing the activity of the Na+, K+-ATPase in vascular smooth muscle cells [12], with possible contribution of increased gene expression of the vascular smooth muscle ATP sensitive potassium channels [4].

Effects of GHD on cardiovascular risk factors and system in adult patients

The relationship between the GH/IGF-I axis and the cardiovascular system is well confirmed by cardiac functional and morphological abnormalities presented by patients with both GH excess and deficiency [1–4]. In particular, patients with hypopituitarism have reduced life expectancy, with a 2-fold higher risk of death for cardiovascular disease compared with healthy controls [13]. It is conceivable that the excessive glucocorticoids or T4 replacement, or gonadal steroids under-replacement can potentially contribute to the increased cardiovascular mortality in hypopituitary patients. Nevertheless, when all other pituitary hormones have been adequately replaced, GHD can be ultimately considered the underlying determinant for the increased mortality observed in these patients [2–4,13]. GHD-mediated negative effects on the cardiovascular function are played both directly on the myocardium and endothelium, and indirectly *via* increased cardiovascular risk factors, hypercoagulability, decreased exercise performance and reduced pulmonary capacity [2–4,14].

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In experimental models [15], hypophysectomy decreases the size of several organs, including the heart, which is reversed by GH administration. GHD patients present different abnormalities in cardiac size and function [2–4]. A significant reduction in the thickness of the left ventricular (LV) posterior wall and of the interventricular septum is reported in both children and adolescents with GHD and in GHD adults, resulting in a decrease of LV mass index (LVMi) and LV internal diameter in these patients [2–4]. Other studies showed, however, a similar cardiac function and morphology between patients developing GHD in adult age (AoGHD) and controls [2–4]. In particular, the decrease in cardiac mass is uncommon in middle-aged or elderly patients, and even in young patients with AoGHD, while it can be mainly observed in young patients with childhood-onset (Co) GHD [16]. Similarly, the so-called hypokinetic syndrome, which is characterized by a decrease in heart rate and systolic performance, was observed only in young GHD patients with CoGHD [2,3]. It should be noted that echocardiography is not a method sensitive enough to reveal subtle deficiency in LV performance. Using the equilibrium radionuclide angiography, our group first reported an impairment of LV performance in response to exercise in most adult GHD patients, regardless of age and age of disease onset [2,3,16]. We found also that cardiac performance was correlated with the GH status, as a significant functional impairment could be evidenced in patients with severe and partial GHD, but not in non-GHD hypopituitary patients [17].

More recently, Boschetti et al. [18] found in a small sample of GHD patients that the coronary flow reserve (CFR), an early marker of impaired myocardial microcirculation that may be present before manifest atherosclerosis and stenosis occur, was significantly decreased as compared to matched controls. New methodologies, such as 2D speckle-tracking echocardiography (2DSTE) [19], have proven to be more sensitive for the detection of subclinical LV dysfunction in several conditions with preserved LV ejection fraction (EF) [20,21]. In this regard, Mihaila [22] recently reported that adult GHD have LV systolic function, assessed by conventional echocardiography, within the normal range, whereas LV longitudinal, circumferential, and torsion functions, assessed by 2DSTE, were impaired, which is suggestive of intrinsic myocardial disease in these patients. Thus, the use of traditional methods of assessment of cardiac impairment might show limited diagnostic accuracy in defining the effects of GHD on cardiac mass [23]. Cardiac magnetic resonance (CMR) imaging, a reliable and reproducible technique for measuring myocardial volume, mass and function, has been used to study a range of cardiomyopathies [24,25]. Currently, there are only few CMR studies assessing the impact of GH deficiency on the heart [26,27,34]. Using CMR, Thomas et al. [27] studied the effects of GHD on myocardial structure and function and found that AoGHD patients have reduced aortic area and LV Mass index (Mi) compared to age- and sex matched healthy controls, but both these cardiac indexes increased after 1 year of GH treatment.

Tipically, adults with GHD have an adverse lipid profile [28]. In particular, increased low-density lipoprotein (LDL) cholesterol and triglycerides have been documented in both sexes, whereas decreased high-density lipoprotein (HDL) cholesterol has been showed only in women, although the increased total cholesterol/HDL ratio occurred both in men and women [28]. Of interest, the severity and duration of GHD is correlated with the adverse lipid profile, with an inverse association emerging between IGF-I and LDL-cholesterol levels [2,3]. Contrariwise, no differences in lipoprotein (a) and apolipoprotein B levels were found between GHD and controls [28,29]. Other cardiovascular risk factors, including increased homocysteine and C-reactive protein levels (CRP) are present in GHD patients [29]. In particular, GHD patients have an approximately 4- to 5-fold increase in CRP [29,30], suggesting the presence of a pro-inflammatory state related to GHD [31,32]. Also, other pro-inflammatory factors may be involved in pathophysiological mechanisms of GHD-related cardiovascular complications. Among them, interleukin (IL-6) and tumor necrosis factor (TNF)-α are well known to play a major role in causing endothelial dysfunction [32]. Increased IL-6 and TNF-α levels have documented in patients with GHD, independently of BMI or obesity [29]. Recently, it has been observed that GHD is associated with altered adipokine protein expression pattern and increased adipocyte diameter, which may predispose white adipose tissue to hypoxia and adipocyte dysfunction, paving the way to the development of the low-grade chronic inflammation [29,33,34]. Conflicting data are available in the literature on leptin levels in GHD patients, and some studies found that its levels were higher in GHD patients than in controls [35–37], while others did not [38]. One study in humans also failed to detect any effect of GH on circulating leptin concentrations [39]. Pregnancy-associated plasma

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protein-A (PAPP-A) was found to be elevated in GHD patients [40]. This may be of particular interest, since PAPP-A is both a cardiovascular risk factor and a mediator of IGF-I bioavailability [40].

GHD is associated with changes in body composition, including reduced lean body mass and increased visceral adiposity [41,42], a phenotype that has been closely linked to insulin resistance and glucose intolerance. Insulin resistance, determined by a decreased insulin-stimulated glucose uptake by fat and skeletal muscle, is an important feature of the metabolic syndrome (MetS) and is associated with low-grade chronic inflammation, endothelial dysfunction and increased cardiovascular mortality [43]. Low, normal and high basal insulin levels have been found in GHD adults, being the degree of obesity a possible confounding factor [14]. In contrast to patients affected by MetS, significantly elevated insulin levels might be not characteristically observed in patients with GHD. However, using the hyperinsulinemic euglycemic clamp method, Johansson et al. [44] showed a 2–3-fold reduction in insulin sensitivity in GHD patients compared with controls, despite normal fasting glucose and insulin levels. As so far, the prevalence of MetS is increased in GHD patients. van der Klaauw et al. [45] documented that GHD patients had a more than 2-fold higher prevalence of MetS when compared with the general population. Also, Attanasio et al. [46] found that MetS prevalence was increased in GHD patients. Interestingly, lean individuals with GHD have larger waist circumference and more abdominal adiposity, with a proportional increase in subcutaneous and visceral tissue with respect to control subjects [33]. Among all these indirect cardiovascular risk factors, abdominal obesity, assessed simply by waist circumference or waist:hip ratio is a well-known negative predictor of subsequent coronary artery disease [47]. Patients with GHD were consistently proven to be affected with centrally distributed adiposity and, additionally, with dyslipidaemia [2–4], the treatment of which becomes crucial in primary and secondary prevention of cardiovascular disease.

Conflicting results have reported in the literature regarding blood pressure (BP) and peripheral resistance in GHD. On the one side, some studies reported slight increases in BP in GHD patients [2–4,48]. The association between GHD and altered BP was confirmed by a large study, which mainly consisted of AoGHD patients without recombinant human rhGH replacement treatment [48]. Similarly, an observational study recruiting almost 1000 GHD patients reported an increased prevalence of hypertension compared to the general population (22% *vs.*15%) [49]. Consequently, GHD was found to be associated with an increased activity of the sympathetic nervous system, with a diastolic BP around 10 mmHg higher in GHD patients than in controls [50]. On the other side, unaltered BP profiles were also reported [51], while BP was even reported to be reduced in young GHD adults [2–4,52]. Likewise, a study from our group failed to document any increase in the prevalence of hypertension in 56 patients classified to have severe GHD compared to sex- and age-matched healthy controls, while showing a decreased systolic BP at peak physical exercise [17]. While circadian BP patterns have been reported to be modified in adult GHD patients [53], a study on 24-h ambulatory BP and circadian rhythm found significant decreases in both systolic and diastolic BP in adult GHD subjects, without any change in circadian rhythm [54].

Conversely, GHD has been consistently found to be associated with vascular endothelial dysfunction and premature vascular atherosclerosis. A decreased formation of NO is reported to occur in untreated GHD patients [55] and, because NO plays a key role in regulating endothelial function and in inhibiting muscle cell proliferation, it is reasonable to hypothesize that a reduced NO synthesis might be implicated in the endothelial dysfunction of patients with GHD. In fact, patients with GHD were shown to have increased carotid intima-media thickness (IMT), one of the earliest morphological changes in the arterial wall in the process of atherogenesis. Markussis et al. firstly showed increased carotid IMT and higher prevalence of atheromatous plaque of common carotid artery in otherwise asymptomatic GHD patients [51]. Afterwards, the association between GHD and increased carotid IMT and/or atherosclerotic plaques, as well as vascular endothelial dysfunction, was confirmed in other series of GHD patients, although with some discrepancies among data [2,3,55,57], likely related to the variability of IGF-I levels in GHD patients. Indeed, it has been found that only patients with IGF-I levels below the normal range presented an increased IMT value and well-defined atherosclerotic plaques at the level of common carotid arteries [2,3]. Although the relationship between premature atherosclerosis and GH and/or IGF-1 deficiency is still far to be completely elucidated, it can be postulated that the presence of IGF-I deficiency *per se* is associated with increased IMT and atherosclerotic plaques at the level of the carotid arteries. As further findings, a number of different markers of vascular and

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endothelial dysfunction [58,59] are reportedly altered in GHD patients, including less distensibility of the aorta and impaired vasodilatory flow [60], disorders in the coagulation and fibrinolytic system components, and abnormalities in inflammatory cardiovascular markers, suggestive of a prothrombotic diathesis [2–4,29]. Notably, some of these abnormalities, mainly hyperfibrinogenemia, fibrinolytic markers, soluble adhesion molecules, and other inflammatory cytokines were more predominant in AoGHD than in CoGHD. Although there is scant evidence on a direct association with the disease severity [2,3,61], these alterations might contribute to the increased prevalence of cardiovascular diseases associated with GHD and could be considered the possible link between GHD, inflammation, and atherosclerosis [29,40].

Effects of rhGH replacement therapy on cardiovascular risk factors and system in adult patients

In spite of existing controversies on cardiovascular impairment of GHD patients, an overall agreement exists in the literature on the ability of GH replacement therapy to improve most cardiovascular risk factors outlined in adult hypopituitary patients [2–4,29]. However, optimal GH dosing and modality of treatment are warranted to maximize the benefits of GH therapy and minimise its potential risks [62].

Robust evidence supports the effectiveness of long-term GH replacement to improve the body composition. GH replacement produces a gradual increases of lean body mass by 2–5 kg and a reduction in fat mass by 30% (approximately 4–6 kg of visceral fat) [63]. The gain in lean body mass is maintained for at least 10 years of GH replacement both in men and women, although the time necessary to detect significant changes may differ between genders. In fact, both men and women lose most of their fat mass in the first year of GH replacement, but men maintained their body weight unaltered over the next nine years of observation, while women regained fat mass during the subsequent two years, after which fat mass remained unchanged until ten years of therapy [64]. Interestingly, changes in body composition appeared to be at least in part sustained after 15 years of therapy [65].

According to the Framingham model, the improvement in body composition reflects a 3–4% decrease in the incidence of coronary heart disease over ten years; thus, this effect of GH replacement therapy represent *per se* the single most important factor in reducing vascular risk [65].

Nevertheless, it has been suggested that dyslipidaemia is the strongest contributor of the excess in cardiovascular risk associated with hypopituitarism [28,29]. Abnormalities in serum lipid concentrations improved with GH replacement therapy, and the same applies to impairment in fibrinolysis [62]. A meta-analysis of blinded, randomized, placebo-controlled trials using low doses and long-duration GH treatment showed that GH replacement has beneficial effects on body composition, total and LDL cholesterol levels, as well as diastolic blood pressure, without significant effects on triglycerides levels [23]. While the positive effect GH therapy on lipid profile was confirmed in a long-term 15-year prospective study (65), another 7-yearr study failed to evidence this beneficial effect [66]. In addition to benefits on serum cholesterol level, GH replacement was shown to improve apolipoprotein B levels in one study [67], while lipoprotein (a) levels increased during GH treatment in others [67,68]. Nevertheless, these unfavorable changes may be outweighed by the beneficial effects of GH replacement on total cholesterol and LDL-C levels. Additional benefits on serum lipid levels may be achieved by combination therapy with GH and statin treatment, and data from KIMS survey suggest that the effect of the concomitant treatments is additive [69].

Globally considering the effects on body composition and lipid profile, a number of studies confirm that long-term treatment with GH improves the constellation of metabolic parameters of MetS [45,46,70–74]. On the other hand, the effects by GH replacement on insulin sensitivity are still debated [75,76]. This controversy might be partially explained by differences in the duration of treatment among the studies, as GH replacement seems to further deteriorate insulin sensitivity in the short-term, namely after 6 weeks; conversely, longer courses of GH treatment were proven to return insulin sensitivity to baseline values through the increase in IGF-1 levels and the reduction of fat body mass [2–4]. Accordingly, in a long-term trial, seven-year GH replacement provided protection from the age-related decline in insulin sensitivity [77]. Among emerging cardiovascular risk factors, it has also reported that GH replacement can improve low-grade inflammation, as documented by a reduction in

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CRP [29,34], TNF-α [78], and IL-6 [34], well characterized inflammatory markers of atherosclerosis. Some positive effects of GH replacement can also be observed for adipokines like adiponectin, leptin [35,36], and pregnancy-associated plasma protein A (PAPP-A), a specific protease whose substrate is IGF-I, which is considered as a biological marker of unstable atherosclerotic plaques [29]. In line with previous studies [79,80], GH replacement exerts positive effects on the sympatho-vagal balance, endothelial function and blood pressure levels in GHD patients, which might contribute to improve their atherosclerotic profile.

In several series of adult GHD patients, GH replacement for 6–24 months was associated with improved IMT at common carotid arteries, reaching levels recorded in controls [2–4,16,56,57], while withdrawal of GH replacement for 6 months in severe GHD adults, but not in adolescents [2,3], was associated with an increase in IMT and further impairment of the cardiovascular risk [16]. Moreover, GH replacement induces a significant increase in flow-mediated dilation, a marker of endothelial function and arterial compliance [2,3]. Cardiac mass is another target of HG therapy and an increase in LV mass is commonly documented in the early phase of GH replacement therapy of GHD adults [2–4,2–4,81,82] as well as children [2,3,83–85]. Amato et al. [83] first showed that GH replacement induced a 26% increase in the LVMi and a 12% increase in the LVEF, which disappeared six months after GH discontinuation. In addition, Ter Maaten et al. [86] found that the hypertrophic effect of GH replacement was short-lasting also during the treatment, as LV mass returned to normal after two years, and similar to pretreatment values after ten-year replacement. In seven adults with AoGHD, 42 months of open GH treatment increased the LV mass and decreased the atrial emptying index, which reflects diastolic function, as compared with healthy matched controls [87].

These results suggest also that patients' age might *per se* promote inappropriate increments in LV mass during long-term GH replacement. However, it should be noted that the doses of GH replacement in these studies were higher than that used currently. In effect, the dose employed during the last decade was reduced from 20 to 26 μg/kg bodyweight in the initial studies to 4–6 μg/kg bodyweight in modern ones.

Together, studies so far published seem to imply that the beneficial effects of current low-dose GH regimens may be counterbalanced by potentially harmful effects of initially-used high GH dose, whereas low-dose individualized GH replacement is effective in improving cardiac function and carries a lower risk of developing cardiac hypertrophy in the long-term [2–4]. However, if an inappropriately high dose of GH is given, there is a risk of an unwanted increment in left ventricular mass, particularly in elderly GHD patients during long-term treatment [2–4].

A few studies did not report any significant change in cardiac mass and performance [2–4]. Contrariwise, we observed a significant increase of the LVEF at peak exercise after 12 month of GH replacement in a cohort of young GHD patients, even if exercise-induced changes of LVEF remained significantly lower than controls after treatment [2,3].

Compared to GHD patients who refused GH replacement, only patients receiving GH replacement showed an improvement of cardiovascular risk parameters, cardiac mass and function parameters after 12 months [2,3]. It should be emphasized, however, that GH replacement, for 12 months is unable to completely normalize cardiac performance, thus indicating that cardiac performance should be monitored in long-term studies. In fact, Chrisoulidou et al. [66] reported a decrease of diastolic blood pressure and an improvement of diastolic filling persisting seven years after GH replacement.

Summary

GH replacement increases cardiac size, not exceeding normal values, improves cardiac performance, more evidently on peak exercise, affects positively body composition and lipid profile, and reduces IMT at common carotid arteries. Despite this large body of evidence on the beneficial effects of GH replacement in GHD patients, however, the most recent interventional studies failed to consistently show GH-mediated improvements in cardiac and prognostic outcomes [88–92]. To weight the beneficial effect of GH replacement in terms of reduced mortality is a relevant clinical issue. Currently, there is no abundance of data regarding the effect of GH replacement on cardiovascular morbidity and mortality [2–4,13,93]. Recently, Gazzaruso et al. [29] underpinned the lack of reliable risk markers in order to attain therapeutic benefit as much as possible by GH replacement, so confirming that more

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accurate prognostic markers have to be identified yet. Furthermore, De Gregorio et al. [94] underlined that hypertension and age are important components of the natural history of GHD and suggested that GH replacement optimization and close follow-up of patients with GHD could reduce the cumulative CV event rates. However, the results of a large registry database showed that GH replacement may be important in adult GHD not only to improve general health and wellbeing, but also to reduce the risk of premature mortality [95]. As the individual changes in the cardiovascular risk factors in all the studies are small and affected by several confounding factors, the global benefit of GH replacement on cardiovascular mortality remains to be determined.

Practice points

- GHD affects heart and the vasculature.
- The role for conventional CV risk factors has not been well established.
- GHD is associated with a number of detrimental factors that affect the cardiovascular system.
- GH replacement improves cardiac size, not exceeding normal values, and cardiac performance.
- Optimizing GH therapy is mandatory to prevent side effects.

Research agenda

- Studies are required to identify accurate prognosticators of cardiovascular risk.
- Studies are required to evaluate whether new imaging techniques have concrete advantages for the assessment of cardiovascular system in clinical practice.
- Further prospective and long-term studies are guaranteed to evaluate the effective reduction of cardiovascular mortality.

Conflict of interest statement

The authors have nothing to disclose.

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